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Investigation of Tenoxicam and γ-Cyclodextrin Binary and Ternary Complexes

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Abstract

Tenoxicam is a widely used non-steroidal anti-inflammatory drug (NSAID). Its complexation with cyclodextrin was studied in order to improve its aqueous solubility and to decrease its side-effects. Two- and three-component systems in several mole-ratios were prepared by means of two different methods. The drug liberation profile, the in vitro membrane diffusion and the *n*-octanol/water partition coefficient were investigated. The presence of complexes was detected via thermoanalytical and X-ray diffractometric studies. On the basis of these data, several compositions were selected for incorporation into topical dosage forms.

Introduction

Tenoxicam (T) is an oxicam derivative belonging to the "enol acid" group; it is a very effective non-steroidal anti-inflammatory drug (Figure 1). The molecule was synthesized in 1976 by Hromatka *et al.* [1] and its pharmacology was investigated by Tanaka and coworkers in 1981 [2]. The three basic therapeutic effects of non-steroidal anti-inflammatory drugs are analgetic, anti-inflammatory and antipyretic; these are attained by the blockage of cyclooxygenase, with a consequent decrease in prostaglandin biosynthesis. There are two cyclooxygenases: COX-1 and COX-2. COX-2 synthesizes the prostaglandins, and is activated in inflamed tissues, induced by cytokines and endotoxins. COX-1 is responsible for the synthesis of prostaglandins in other tissues (stomach, kidney, blood vessels, thrombocytes, etc.) in the organism. Most NSAID compounds block both COX-1 and COX-2. The blockage of COX-2 results in anti-inflammatory, antipyretic and analgetic effects, while that of COX-1 is responsible for ulcerogenic side-effects.

Tenoxicam did not show mutagenic, carcinogenic or teratogenic side-effects in animal tests. Some kidney and gastrointestinal effects, deviations in muscle contractility and a delay of birth delivery were experienced in animal toxicology investigations. It is less toxic than piroxicam.

Tenoxicam is recommended in several types of chronic arthritis, tendovaginitis and sprain, and to relieve postoperative pain, among other indications [3–7].

The half-life of tenoxicam is 72 hours, and it is therefore administered once daily. A daily dose of 20 mg of *Tilcotil* tablet is generally well tolerated. Approximately

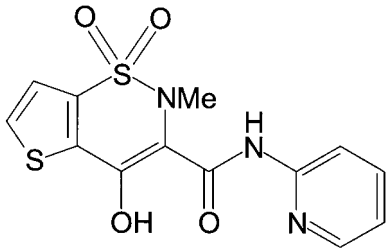

Figure 1. Chemical structure of tenoxicam.

12.5% of patients display side-effects or alterations in laboratory data. The symptoms are manifested only very slightly and temporarily. The treatment is stopped because of these side effects in only 1% of the patients. The most frequent side-effects are gastrointestinal effects (11%): heartburn, nausea, diarrhoea and constipation; central nervous system effects (3%); dermal effects (1–2%): pruritus, spots, photodermatosis and skin irritation; renal effects (1–2%): increased urea-N and creatinine concentrations; liver effects (1–2%): increased SGOT, SGPT,γ-GT and bilirubin levels; and rarely granulocytopenia, a decreased haemoglobin level and Stevens-Johnson-Lyell-syndrome [8–11]. Complex treatment based on pharmacological methods has been developed to decrease these side-effects [12]. Dissolution of tenoxicam was increased by using β-cyclodextrin [13, 14] The present work deals with the stage of formulation of different dosage forms.

Table 1. Influence of CD derivatives on the UV spectrum of tenoxicam (%)

1. Tenoxicam (T)	100
2. T + α-CD	136
3. T + β-CD	182
4. T + γ-CD	218
5. T + ME-β-CD	198
6. T + DIMEB	218
7. T + RAMEB	219
8. T + HE-β-CD	132
9. T + HP-β-CD	192

Experimental

Materials

Tenoxicam: 4-hydroxy-2-methyl-N-2-pyridinyl-2H-thienol[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide (Hoffmann–La Roche AG., Basel, Switzerland); α-, β- and γ-cyclodextrin (CD), dimethyl-β-CD (DIMEB), random-methyl-β-CD (RAMEB), hydroxypropyl-β-CD (HP-β-CD) (Cyclolab R&D. Laboratory, Budapest, Hungary); hydroxyethyl-β-CD (HE-β-CD), methyl-β-CD (ME-β-CD) (Wacker-Chemie GmbH, Munich, Germany), DL-malic acid (MA), sodium chloride, potassium dihydrogenphosphate, disodium hydrogenphosphate, glycocoll and hydrochloric acid (Reanal, Budapest, Hungary).

Tartaric acid (TA), citric acid (CA) and solvents (ethanol, methanol, etc.) are official in *Pharmacopoeia Hungarica VII* [15].

Apparatus

USP rotating-basket dissolution apparatus [16], type DT; kneading mixer, type LK5 (Erweka Apparatebau GmbH, Heusenstamm, Germany), Unicam UV2 UV/Vis Spectrometer (Unicam Ltd., Cambridge, England); Sartorius membrane diffusion apparatus (Sartorius-Membranfilter GmbH, Göttingen, Germany), STD 2960 Simultaneous DTA TGA and DSC 2920 Modulated DSC instruments, and a Philips PW-1830 X-ray diffractometer.

Preliminary experiments

The effects of the different CD derivatives on the solubility of the active agent were determined: a mixture of 0.03 g of tenoxicam and 0.50 g of CD derivative was mixed with water to 20.0 g and stirred for 10 min with a magnetic mixer. Suspension systems were filtered through filter paper and, after suitable dilution, the UV spectra were recorded. A system without CD was used as a control. DIMEB, RAMEB, and γ-CD had the greatest influence on the solubility of the active agent (Table 1): the solubility was increased by a factor of 2.18. γ-CD was chosen for further examinations.

The absorption maximum of the active agent was determined (364 or 368 nm, depending on the pH). The calibration plot revealed that the absorption obeys the Bouguer–Lambert–Beer law in the concentration interval 0–16 μg g^{-1}. The molar extinction coefficients (ϵ) were 64.26 (artificial gastric juice), 46.15 (artificial intestinal juice) and 47.68 (artificial plasma).

Preparation of products

The two-component products were prepared in four different mole ratios (drug : CD mole ratio = 2 : 1, 1 : 1, 1 : 2 and 1 : 3), and the ternary systems were prepared in three different mole ratios (drug : CD : organic acid = 1 : 1 : 1, 1 : 2 : 2 and 1 : 3 : 3).

Physical mixtures (PM): The ground components were mixed in a mortar and sieved through a 100 μm sieve.

Kneaded products (KP): Physical mixtures of the drug and γ-CD were mixed (Erweka LK5) in the same quantity of ethanol + water (1 : 1). They were kneaded until the bulk of the solvent mixture had evaporated. After this, they were dried at room temperature and then at 105 °C, and were next pulverized and sieved through a 100 μm sieve.

Products were stored under normal conditions at room temperature in closed glass containers.

Dissolution studies

In the USP rotating-basket dissolution apparatus, 50 mg of pure tenoxicam, binary products containing 50 mg of drug or ternary products containing 300 mg of drug, were examined in 900.0 g of artificial gastric juice or intestinal juice. The basket was rotated at 100 rpm. Sampling was performed after 5, 10, 15, 30, 60 and 90 min. The volume of one sample was 5.0 mL. The tenoxicam contents of the samples were determined spectrophotometrically after filtration and dilution.

Membrane diffusion experiments

Stricker's Sartorius instrument was used [17, 18]. Measurements were performed from 100.0 mL of artificial gastric juice or artificial intestinal juice into artificial plasma (Table 2). 50 mg of active agent, or product containing 50 mg of tenoxicam was in the donor phase in all cases. The temperature was 37.5 ± 1.5 °C. 5.0 mL sample aliquots were taken five times (after 30, 60, 90, 120 and 150 min) and their active agent contents were determined spectrophotometrically after filtration and dilution. The amount of diffused active agent and the diffusion constant K_d were calculated:

$$K_d = \frac{c_{\mathrm{II}_2} - c_{\mathrm{II}_1}}{T_2 - T_1} \cdot \frac{1}{C_{\mathrm{I}_0}} \cdot \frac{V_{\mathrm{II}_0}}{F} \quad [\mathrm{cm\ min^{-1}}],$$

where c_{II_x} is the corrected drug concentration in phase II at time T_x (mg mL^{-1}); V_{II_0} is the volume of the aqueous phase II at time T_0 (100 mL); F is the surface area of the membrane (cm^2); T_x is the time (min); and c_{I_0} is the theoretical initial drug concentration in phase I (mg mL^{-1}) [17].

Table 2. Composition of artificial juices

		Gastric juice	Intestinal juice	Plasma
pH (±0.1)		1.1	7.0	7.5
1N HCl	(g)	94.0	–	–
NaCl	(g)	0.35	–	–
Glycine	(g)	0.50	–	–
$Na_2HPO_4 \cdot 2H_2O$	(g)	–	14.4	20.5
KH_2PO_4	(g)	–	7.1	2.8
NaOH	(g)	–	–	–
Distilled water	to		1000 ml	

Determination of the n-octanol/water partition coefficient

Tenoxicam or products containing tenoxicam were dissolved in water-saturated *n*-octanol and in *n*-octanol-saturated water. Further drug or CD product was added to this system during continuous mixing until the excess drug appeared in suspended form. After filtration these saturated systems were diluted with *n*-octanol-saturated distilled water or water-saturated *n*-octanol and the active agent content was determined spectrophotometrically.

Thermoanalytical methods

Thermogravimetry (TG), derivative thermogravimetry (DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) were used as thermoanalytical methods to confirm the presence of inclusion complexes.

CDs generally lose water below 100 °C, and decompose above 250 °C. The DSC method can therefore be used if the crystallized drug melts in the temperature range between the temperature of water loss from the CD and the temperature of its decomposition (120–250 °C).

A distinction can be made between surface adsorption and inclusion complex formation by means of thermoanalytical methods. The presence of an inclusion complex is shown indirectly by changes (e.g., in evaporation, thermal decomposition, oxidation, melting or polymorphism) relative to the non-complexed free drug. Approximately 2–5 mg of active agent or product containing 2–5 mg of tenoxicam was examined between 25 °C and 300 °C. The heating rate was 5 °C min^{-1}. The argon flow rate was 10 L $hour^{-1}$.

X-ray investigations

The X-ray spectra were measured on a Philips PW-1830 diffractometer (CuK_α radiation, λ =1.54 nm) in the interval 2θ = 8–30 °. The spectra were taken of the pure drug, γ-CD, citric acid and selected compositions immediately after preparation.

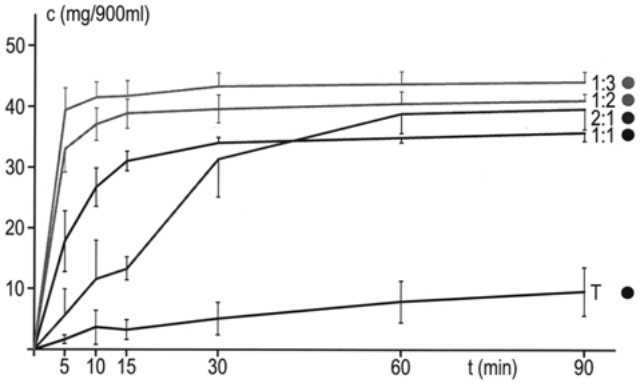

Figure 2. Dissolution of Tenoxicam from physical mixtures (artificial gastric juice).

Results

Dissolution studies

Binary products

All the dissolution data on the investigated products were better than those for the pure drug. There was no significant difference between the dissolved drug amount, but differences in dissolution rate were experienced.

The pure drug dissolves better in artificial intestinal juice (25.3 mg into 900 mL in 90 min) than in artificial gastric juice (9.7 mg into 900 mL in 90 min).

The solubility of the physical mixtures in artificial gastric juice was increased 3.5–5-fold when CDs were used (Figure 2). The mole ratio influenced the dissolution rate. Saturation was measured for the lowest CD content at 60 min, but at 15–30 min at higher CD concentrations. The maximum dissolution rate was experienced with the 1 : 3 product.

While the solubility increase in artificial intestinal juice was not so high (1.8-fold as compared to that of the pure drug), the dissolved drug amount was slightly higher than in the case of artificial gastric juice. This can be explained by the fact that pure tenoxicam dissolves better in the intestinal juice. A difference between the products was observed only in the dissolution rates.

A significant (4.5-fold) solubility increase was measured for the kneaded products in artificial gastric juice (Figure 3). No significant difference between the curves can be seen in the Figure. The dissolution rate was lower in all cases as compared to the physical mixtures.

A 1.6–1.8-fold solubility increase was found in the case of artificial intestinal juice, which is a result of the solubility of the tenoxicam, similarly as for the physical mixtures. It is worthy of mention that the 1 : 3 physical mixture was the best of all in artificial gastric juice, whereas in artificial intestinal juice the solubility of this product was the worst.

Finally, it can be concluded that the presence of γ-CD, and not the preparation method, increases the dissolved drug amount; a difference can be measured only in the dissolution rate.

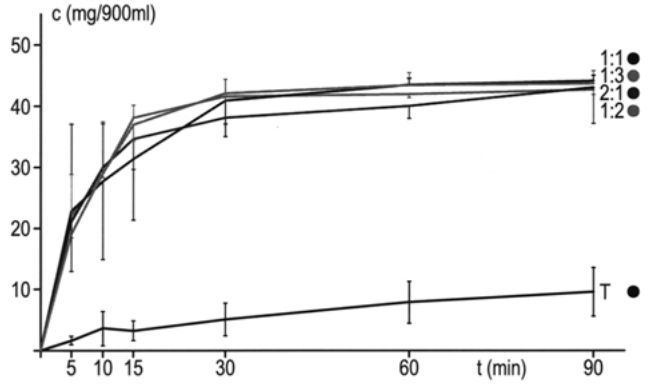

Figure 3. Dissolution of Tenoxicam from kneaded products (artificial gastric juice).

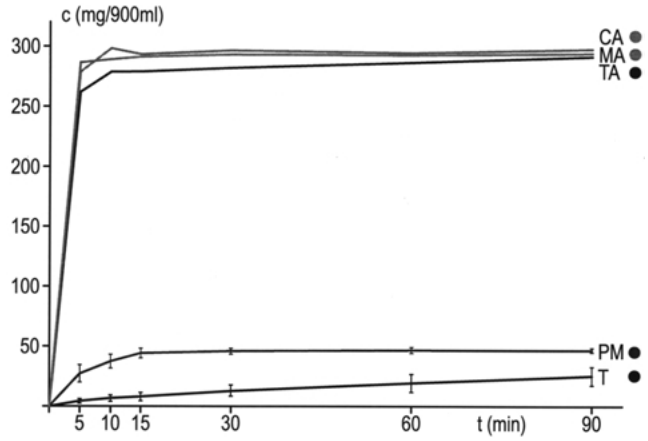

Figure 4. Dissolution of Tenoxicam from ternary physical mixtures (artificial intestinal juice).

Ternary systems

The dissolution profile of the ternary complexes is significantly better than that of the binary systems, and products with higher drug content (300 mg tenoxicam) were therefore investigated. Figures 4 and 5 show the dissolution curves. These data were significantly higher than those for the binary systems or the pure drug. While the total amount of incorporated drug was liberated in the case of artificial intestinal juice, only 1/3 of the drug dissolved in artificial gastric juice.

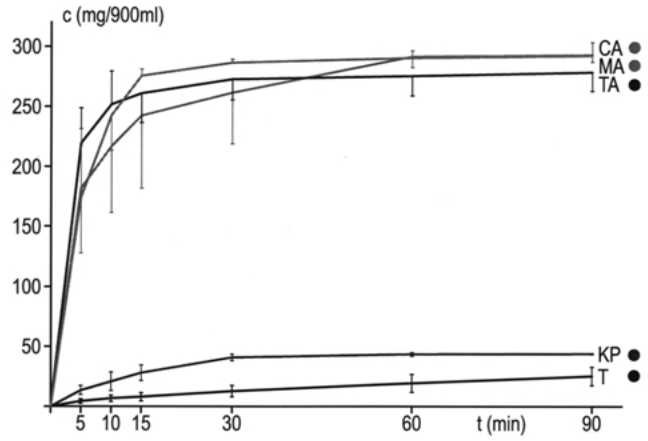

Figure 5. Dissolution of Tenoxicam from ternary kneaded products (artificial intestinal juice).

Table 3. Membrane diffusion examinations of physical mixtures

Products	From gastric juice			From intestinal juice		
	K_d (10^{-4}) [cm/min]	S	Diff. %	K_d (10^{-4}) [cm/min]	S	Diff. %
T	7.47	1.51	4.98	16.96	3.69	11.31
2 : 1	7.90	0.66	5.27	16.36	2.75	10.91
1 : 1	5.28	1.11	3.52	16.61	3.61	11.07
1 : 2	5.89	0.73	3.93	15.60	3.83	10.40
1 : 3	5.87	0.38	3.91	16.59	2.62	11.06

S = Standard deviation.

More than a 12-fold increase in solubility in artificial gastric juice was measured for the physical mixtures, while a 11.5-fold increase occurred in artificial intestinal juice (Figure 4) as compared to the pure drug. The chemical identity of the organic acid used did not influence the results.

The solubility increase achieved for the kneaded products (similarly as for the physical mixtures) was around 13-fold, while in artificial intestinal juice (Figure 5) the solubility increase was 11-fold. The standard deviation of the parallel measurements was very high at the beginning of the dissolution experiments, but gradually decreased. Very low standard deviation values were calculated at 90 min. This can be explained in that the sample withdrawn was not from a homogeneous phase and accordingly the sample concentration did not represent the acceptor phase. It is very interesting that, although citric acid was the best in increasing the solubility, and tartaric acid was the worst from this point of view, citric acid exhibited the lowest dissolution rate.

To summarize these results, it can be concluded that the organic acids used increased the solubility independently of their chemical constitution. The dissolved drug amount was not influenced by the preparation method. A very high dissolution rate was measured, especially for the physical mixtures. The concentration of dissolved tenoxicam did not differ in artificial gastric and intestinal juice in case of the binary systems; when the acids were added, the dissolution decreased in the low-pH gastric juice.

Membrane diffusion examinations

Binary products

Tables 3 and 4 illustrate the diffusion rate constants and the percentage diffused drug amounts (measured at 150 min).

When the diffusion from artificial gastric juice into artificial plasma was studied, the diffused drug amount and the diffusion rate constant slightly increased for the 2 : 1 product; the ratios 1 : 2 and 1 : 3 led to similar results, and the 1 : 1 ratio displayed a significant decrease.

No significant change was found in the diffusion from artificial intestinal juice into artificial plasma as compared to the data on pure tenoxicam. A slight decrease in diffusion was experienced for all of the products.

A slight decrease in diffusion rate constant relative to the pure drug data is an advantage from a bioavailability point

Table 4. Membrane diffusion examinations of kneaded products

Products	From gastric juice			From intestinal juice		
	K_d (10^{-4}) [cm/min]	S	Diff. %	K_d (10^{-4}) [cm/min]	S	Diff. %
T	7.47	1.51	4.98	16.96	3.69	11.31
2 : 1	5.14	0.46	3.43	15.21	5.25	10.14
1 : 1	8.00	1.91	5.33	12.91	7.33	8.61
1 : 2	10.32	0.84	6.88	9.67	3.49	6.45
1 : 3	9.08	1.63	6.05	8.86	2.70	5.90

S = Standard deviation.

Table 5. Membrane diffusion examinations of physical mixtures

Products	From gastric juice			From intestinal juice		
	K_d (10^{-4}) [cm/min]	S	Diff. %	K_d (10^{-4}) [cm/min]	S	Diff. %
T	7.47	1.51	4.98	16.96	3.69	11.31
1 : 1	5.28	1.11	3.52	16.61	3.61	11.07
MA	6.17	0.39	4.11	13.40	3.51	8.93
TA	6.01	0.61	4.01	15.20	3.71	10.14
CA	5.79	0.71	3.86	15.18	2.83	10.12

S = Standard deviation; MA = malic acid; TA = tartaric acid; CA = citric acid.

of view, as the applied CD derivative does not appreciably hinder the absorption of the drug through the membranes.

Considerable alterations were found with the kneaded products. A decreased diffusion was observed for the 2 : 1 product in artificial gastric juice, while increases were experienced for the others. The highest increase was found at a mole ratio of 1 : 2.

Measurement of the diffusion from artificial intestinal juice to artificial plasma revealed that, on increase of the CD content, the tenoxicam amount that diffused through the lipophilic membrane decreased, and the rate constant of this process also decreased.

Ternary systems

Tables 5 and 6 illustrate the diffusion rate constants and the percentage amount of drug diffused (measured at 150 min).

A decrease in the diffusion from artificial gastric and intestinal juice was found for the ternary systems as compared to the pure drug data. The diffused drug amount and the diffusion rate constant decreased to the same extent in the first case; tartaric acid and citric acid reduced the diffusion values only slightly, whereas malic acid did so significantly.

Table 6. Membrane diffusion examinations of kneaded products

Products	From gastric juice			From intestinal juice		
	K_d (10^{-4}) [cm/min]	S	Diff. %	K_d (10^{-4}) [cm/min]	S	Diff. %
T	7.47	1.51	4.98	16.96	3.69	11.31
1 : 1	8.00	1.91	5.34	12.91	7.33	8.61
MA	6.43	1.47	4.29	13.85	3.65	9.23
TA	7.78	3.06	5.24	15.19	3.27	10.12
CA	7.79	0.48	5.26	14.51	3.08	9.67

S = Standard deviation; MA = malic acid; TA = tartaric acid; CA = citric acid.

Table 7. n-octanol/water partition coefficient of binary complexes

Products		Partition coefficent	c_{octanol} (μg/ml)	c_{water} (μg/ml)
T		3.066	194.52	63.44
PM	2 : 1	2.244	192.95	85.99
	1 : 1	2.463	192.42	78.12
	1 : 2	2.322	191.37	82.84
	1 : 3	2.179	190.85	87.56
KP	2 : 1	3.122	229.12	73.40
	1 : 1	2.779	224.40	80.74
	1 : 2	2.180	196.62	90.18
	1 : 3	1.146	197.66	172.50

Citric acid and tartaric acid slightly increased the amount of drug that diffused through the lipophilic membrane and also the diffusion rate constant in artificial gastric juice. All of the organic acids reduced the diffusion in artificial intestinal juice, least of all tartaric acid, and most strongly malic acid.

In summary, it may be stated that the presence of γ-CD did not significantly affect the drug amount that diffused or the diffusion rate constant. The increased aqueous solubility and the constant diffusibility are advantageous from a bioavailability aspect. Constant diffusibility was supported by the values of the n-octanol/water partition coefficients.

n-Octanol/water partition coefficient

The solubility of the products in n-octanol did not change with increasing CD ratio. The aqueous solubility increased slightly for the physical mixtures, and with increasing CD content for the kneaded products.

The presence of CD in the products decreased the n-octanol/water partition coefficient: an increased aqueous solubility was obtained as compared to that for the pure drug. On the basis of constant n-octanol solubility data, a similar diffusion capacity is expected, as the diffusibility is directly proportional to the lipophilicity (Table 7).

Thermoanalytical examinations

The thermoanalytical curves of tenoxicam and γ-CD, physical mixtures and kneaded binary products with tenoxicam: γ-CD ratios of 2 : 1, 1 : 1, 1 : 2, 1 : 3 and tenoxicam: γ-CD : MA, tenoxicam: γ-CD : TA, tenoxicam: γ-CD : CA ternary physical mixtures and kneaded products with ratios of 1 : 1 : 1, 1 : 2 : 2 and 1 : 3 : 3 were recorded. The DSC plots and their evaluation are discussed in detail on the basis of the thermoanalytical tests.

Tenoxicam melted at around 220 °C and decomposed immediately, as seen in the DSC plot. No change can be

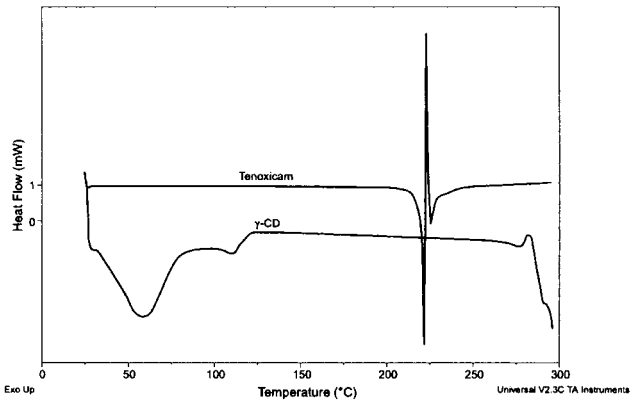

Figure 6. DSC curve of Tenoxicam and γ-CD.

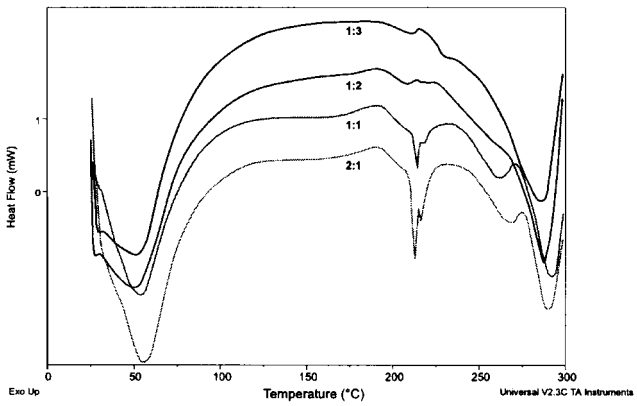

Figure 7. DSC curves of kneaded products.

seen in the DSC curve of γ-CD in this temperature range (Figure 6).

The DSC curves of the binary physical mixtures are the sums of the curves of the two components, containing both peaks representative of γ-CD and tenoxicam itself. There is no signal indicating a thermally induced interaction between the two components. The exothermic peak of tenoxicam decreases with increasing CD content. It may be stated that the tendency of the active agent to decompose can be reduced by increasing the concentration of the auxiliary material.

The DSC curves of the binary kneaded products show an exothermic peak before the melting point. This can be explained by the thermally induced crystallization of the amorphous part of the CD. The endothermic peak representing "*free*" tenoxicam can be found at the higher ratios of 2 : 1 and 1 : 1. The maximum temperature values shift towards lower temperatures. The melting peak of tenoxicam (if free tenoxicam is present) disappears for the 1 : 2 and 1 : 3 products, and complex formation is therefore presumed (Figure 7).

The DSC curve of the 1 : 1 : 1 kneaded product containing citric acid (Figure 8) exhibits the tenoxicam peak, which means that there is no interaction between the components. The 1 : 2 : 2 and 1 : 3 : 3 kneaded products were also prepared, and (as for the binary products) the peak of tenoxicam is missing, confirming inclusion complex formation.

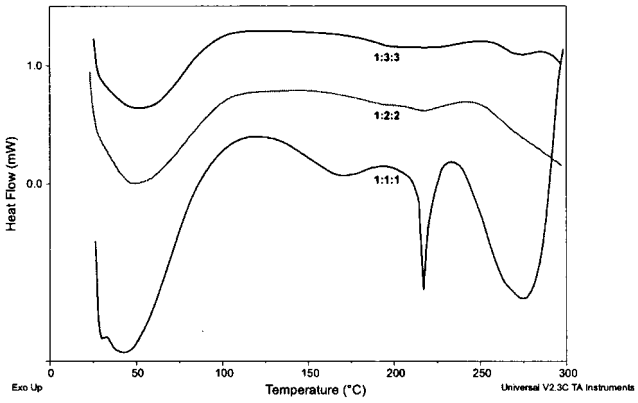

Figure 8. DSC curves of ternary kneaded products.

X-ray investigation

The X-ray spectra were recorded to support the findings of the investigation of the dissolution quantity and rate and the diffusion studies. Higher dissolution results and rates and higher diffusion results were observed for those products for which the presumably amorphous part of the active ingredient was more extensive. As may be seen in Figure 9, tenoxicam, γ-CD and especially citric acid had crystalline structures, while the selected products (2 : 1 and 1 : 3 kneaded products; and 1 : 1 : 1 and 1 : 3 : 3 kneaded products with CA) were amorphous. The amorphous part of the products increased with increasing CD content.

Conclusions

Our results can be summarized as follows:

- CD derivatives improve the solubility of tenoxicam; the highest efficacy was experienced for DIMEB and γ-CD.
- Binary and ternary products of tenoxicam and γ-CD were prepared and examined.
- Significant solubility and dissolution rate increases were measured for the binary products as compared to the pure drug; these were 4–5-fold for artificial gastric juice. The preparation method and the composition did not influence the amount of dissolved drug significantly; the difference was manifested in the duration of dissolution.
- An organic acid used to make ternary products increased the solubility considerably. The drug amount that dissolved did not depend on the chemical identity of the organic acid or on the preparation method. The pH of the dissolution medium had a considerable effect on this process: a 7-fold solubility increase was measured in the case of artificial intestinal juice, and a 3-fold one for artificial gastric juice, as compared to the results for the binary products.
- The presence of CD influenced the amount of drug that diffused and the diffusion rate constant only slightly or not at all under in vitro conditions.
- The *n*-octanol/water partition coefficient decreased with increasing CD content. A major improvement in aqueous solubility was experienced with constant *n*-octanol solubility.

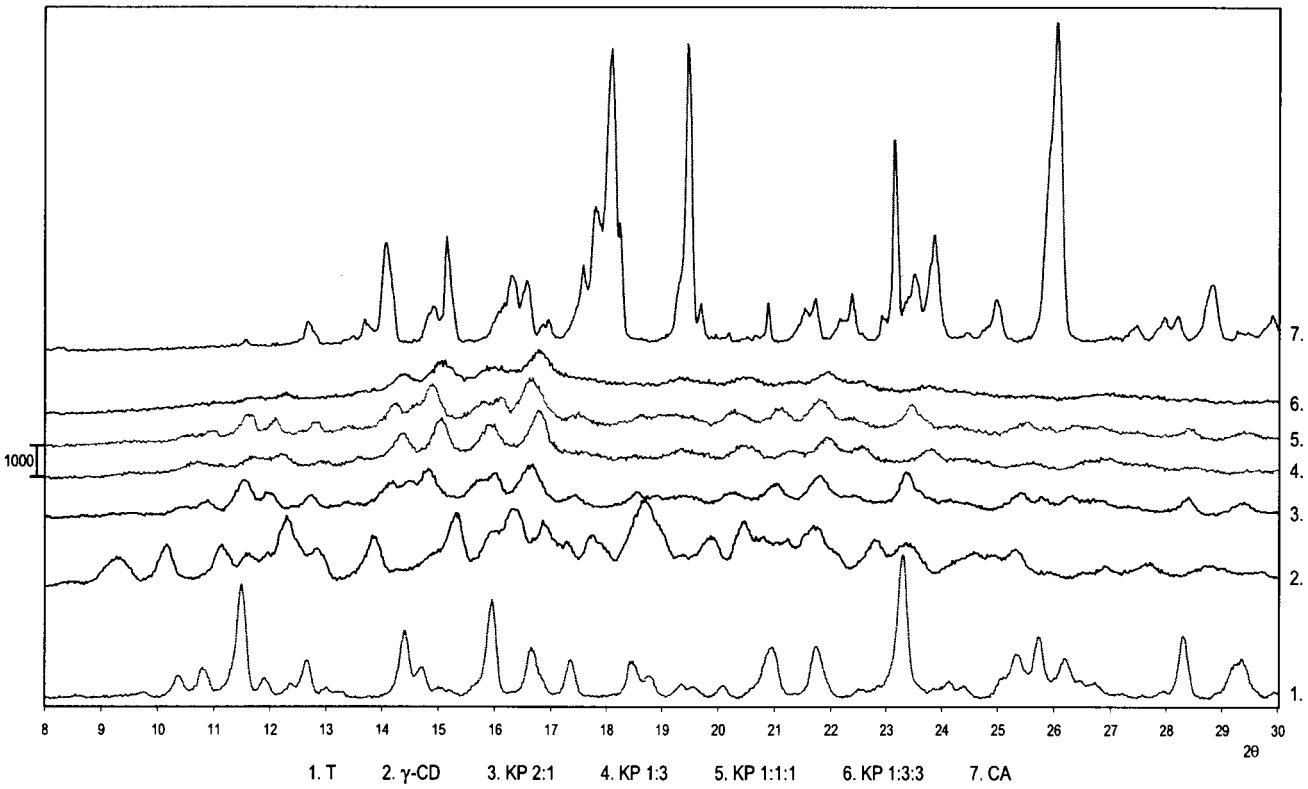

Figure 9. X-ray diffractograms of Tenoxicam, γ-CD, citric acid and their products.

- Inclusion complex formation was checked by means of DSC studies for the 1 : 2 and 1 : 3 binary, and the 1 : 2 : 2 and 1 : 3 : 3 citric acid-containing ternary kneaded products.
- X-ray studies demonstrated that the kneaded products exhibited an amorphous structure.
- The 1 : 1 binary and the 1 : 1 : 1 ternary products were selected for further investigations on the basis of these results.

Acknowledgements

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